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Inflammation and scarring form a positive feedback loop in trachoma

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Scar tissue from people with the world's leading infectious cause of blindness has a distinctive molecular footprint, according to new results published in *Scientific Reports* and *PLOS*. The research points to immune system activity in people with scarring trachoma in the absence of infection and potential targets for treatment. The two studies were carried out by collaborative teams at the UCL Institute of Ophthalmology, Moorfields Eye Hospital and the London School of Hygiene and Tropical Medicine, with funding from Fight for Sight.

Trachoma begins with repeated childhood infection of the eyelid's lining (the conjunctiva) by Chlamydia trachomatis bacteria. It can progress into adulthood with long-term inflammation and scarring, even while there is no detectable infection. Scarring tightens the eyelids and turns the lashes inward (trichiasis), where they scratch the eye's surface (the cornea), causing pain and eventual blindness. The condition is endemic in 51 countries and the cause of irreversible blindness in 1.2 million people.

Dr Maryse Bailly at UCL Institute of Ophthalmology led the study published today in *Scientific Reports*. The team has shown that connective tissue cells (fibroblasts) grown from the biopsies of patients undergoing eyelid surgery produce higher levels of immune system signalling molecule interleukin 6 (IL-6) compared to normal conjunctival fibroblasts.

"IL-6 is an important mediator of inflammation and a previously suggested risk factor for scarring trachoma," said Dr Jenny Kechagia,

first author of the study. "Our results show that although IL-6 does not stimulate tissue contraction directly, it activates immune cells (macrophages), which in turn stimulates fibroblast contraction and may drive local inflammation. This positive feedback loop between scarring and inflammation may contribute to chronic scarring and suggests that the conjunctival stroma (connective tissue) itself may play a more central role in scarring trachoma than previously thought."

Recent Fight for Sight PhD student Dr Tamsyn Derrick is first author of the study published in *PLOS* and led by Dr Matthew Burton at the London School of Hygiene and Tropical Medicine. The team found that compared to healthy controls, eyelid tissue from people with scarring trachoma contains significantly more of the pro-inflammatory signalling molecules IL-1ß and S100A7 and pro-scarring connective tissue growth factor (CTGF). There was evidence of ongoing inflammation in the stroma of individuals with trichiasis even when this inflammation was not externally visible on the patient's eyelid, consistent with the local inflammatory feedback loop proposed by Dr Jenny Kechagia.

"CTGF modulates the interaction between cells and the connective tissue , and over activity of CTGF is known to drive scarring disease in the heart, lung and kidney, said Dr Derrick. "Our data suggest that ongoing inflammation in the conjunctiva is associated with CTGF activation, which in turn drives fibrosis and scarring. As a potential direct mediator of inflammation-induced scarring in the conjunctiva, CTGF could be a suitable target for treatment to halt the progression of scarring trachoma."

Dr Dolores M Conroy is Director of Research at Fight for Sight. She said: "The World Health Organisation estimates that 231 million people live in the regions where trachoma is widespread. Trachoma control programmes do a good job of treating the active infection with antibiotics, however there are a great many people at still risk of

progressing to scarring trachoma given that the condition can persist once the infection has gone. In order to develop a treatment that can prevent the chronic inflammation and scarring that lead to blindness, we need to understand how the two are linked. Results from both these studies take us an important step in the right direction."

More information: Kechagia, J.Z. et al. Fibroblasts profiling in scarring trachoma identifies IL-6 as a functional component of a fibroblast-macrophage pro-fibrotic and pro-inflammatory feedback loop. *Sci. Rep*. 6, 28261; DOI: 10.1038/srep28261 (2016).

Derrick T, Luthert PJ, Jama H, Hu VH, Massae P, Essex D, et al. (2016) Increased Epithelial Expression of CTGF and S100A7 with Elevated Subepithelial Expression of IL-1β in Trachomatous Trichiasis. *PLoS Negl Trop Dis* 10(6): e0004752. DOI: 10.1371/journal.pntd.0004752

Provided by Fight for Sight